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Can endometrial injury increase the success of clomiphene citrate in achieving pregnancy?

Endometrial injury and clomiphene citrate

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Abstract
Aim: The aim of the study is to observe whether endometrial injury has an effect on pregnancy success in patients who are scheduled for timed intercourse after ovulation induction with the use of clomiphene citrate in patients with unexplained infertility.
Material and Methods: The study was planned as a prospective randomized controlled trial with 215 patients, 105 patients in the injury group and 110 patients in the control group. All patients had unexplained infertility. In the injury group, endometrial injury was performed, before the ovulation induction cycle, in the mid-luteal phase. No intervention was performed on the patients in the study group before the treatment cycle. Ovulation induction was initiated by administering 100 mg/day clomiphene citrate and after follicle development, human chorionic gonadotropin (hCG) was administered to the patients in both groups and timed intercourse (36 hours after hCG) was planned for all patients.
Results: It was observed that 27 (25.7%) patients in the injury group and 19 (17.3%) patients in the control group could achieve pregnancy, 21 (20%) of these patients in the injury group and 14 (12.7%) patients in the control group were able to achieve clinical pregnancy. As a result, although both pregnancy and clinical pregnancy rates were found to be increased in the injury group, this increase was not statistically significant.
Discussion: Much larger and more comprehensive studies are needed to show that adding endometrial injury to treatment with clomiphene citrate, which is an extremely cost-effective and easy procedure, can actually increase pregnancy rates.

Keywords
Ovulation, Induction, Clomiphene, Injury

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Introduction

Infertility is still an important health concern in women nowadays. Clomiphene citrate is one of the first-line drugs that are used, especially in the treatment of unexplained infertility, because it is cheap, easy to use, and has few side effects [1, 2]. Clomiphene citrate is an estrogen receptor antagonist that increases follicular growth by increasing follicle-stimulating hormone release, as well as triggering luteinizing hormone (LH) peak by creating a negative feedback effect in the estrogen signaling pathway and thus triggering ovulation [3]. Although it is generally successful in triggering ovulation, pregnancy rates achieved with clomiphene citrate are less due to its anti-estrogenic effects on the endometrium [1]. Hence, scientists are looking for ways in which the anti-estrogenic effect of clomiphene citrate use can be prevented.

According to the literature, endometrial injury emerges as a new method that facilitates the attachment and implantation of the embryo to the endometrium, and it is seen that majority of the studies on endometrial injury are aimed at increasing the success of implantation in patients with repeated unsuccessful in vitro fertilization (IVF) cycles [4-7]. Local endometrial injury (i.e., mechanical trauma to the endometrium) causes the secretion of various cytokines and adhesion molecules that are thought to facilitate implantation and embryo adhesion by increasing endometrial receptivity [4, 8]. However, many recent studies have demonstrated that adding injury to every IVF cycle in routine practice does not provide any benefit to pregnancy rates, and recommends limiting the injury procedure only to patients with implantation failure [9, 10]. Considering the use of clomiphene citrate, despite the high ovulation rates, it is noteworthy that the pregnancy rates and the implantation success are low due to the effects of clomiphene citrate on the endometrium [11, 12]. Based on this, it can be thought that adding endometrial injury to the clomiphene citrate treatment, which is cost-effective and easy to use, will overcome the endometrial adverse effects caused by clomiphene citrate, increase the effectiveness, and facilitate embryo implantation. The aim of the study is to observe whether endometrial injury has an effect on pregnancy success in patients who are scheduled for timed intercourse after ovulation induction with the use of clomiphene citrate in patients with unexplained infertility.

Material and Methods

The study was planned after the permission of our University Medical Faculty Ethics Committee. We evaluated 230 patients who were admitted to our gynecology and obstetrics outpatient clinic with unexplained infertility. Six patients were excluded because they did not agree to participate in the study or did not fully meet the inclusion criteria. The remaining patients were randomized into two groups (injury group and control group), including 112 participants each. We excluded 6 patients from the injury group and 2 patients from the control group from the study because they did not complete their follow-up or because they were resistant to clomiphene citrate (follicle did not develop with the use of clomiphene citrate). Also, one patient grew 3 follicles in the injury group and was excluded from the study. Thus, the study was performed on a total of 215 patients, 105 patients in the injury group6 and 110 patients in the control group.

The study was planned as a prospective randomized controlled trial. Informed consent was obtained from all participants included in the study. The inclusion criteria for the study were determined as follows: Age group between 18 and 38 years, no chronic comorbidities, no pathological findings on ultrasonography, no basal hormone level disturbances on the third day of menstruation, no previous infertility treatment, body mass index value between 18.5-24.9, normal findings on hysterosalpingography, and the partner having normal spermiogram values according to the WHO criteria [13]. The patients who did not develop follicles after treatment or who developed more than two follicles were excluded from the study. All patients included in the study were divided into two groups, i.e., study and control groups.

Treatment Protocol

The patients were randomized into two groups, namely the injury group and the control group. In the injury group, the same researcher performed the endometrial injury procedure on the posterior wall of the uterine cavity, by moving the curette back and forth for one time, in a sterile manner using a Novak curette before the treatment cycle of the patients, in the mid-luteal phase (between the 21st and 24th days of the cycle). In order not to disrupt the implantation by causing excessive damage to the endometrium, the injury procedure was preferred to be performed in the cycle before ovulation induction. No intervention was performed on the patients in the control group before the treatment cycle. Ovulation induction was initiated by administering 100 mg/day clomiphene citrate (Klomen 50 mg tablet, Kocak Farma Pharmaceutical and Chemical Industry Co., Ltd., two doses per day, orally) for 5 days starting on the 3rd, 4th, or 5th day of the treatment cycle. A successful ovarian response was considered as the formation of one or two follicles of size 18 mm or more, 3–5 days after the completion of clomiphene citrate and was evaluated by transvaginal ultrasonography. After proper follicle development, human chorionic gonadotropin (hCG) (Ovitrelle 250 mcg / 0.5 mL, Merck Pharmaceutical and Chemical Industry Co., Ltd., single-dose, 6500 IU hCG, subcutaneous) was administered to the patients in both groups and timed intercourse was planned for all patients 36 hours after hCG for ovulation. Patients who did not develop follicles or developed more than two follicles after clomiphene citrate were excluded from the study.

On the 14th day after coitus, the serum beta-hCG values of the patients were measured for determination of pregnancy. Transvaginal ultrasound was performed on pregnant patients at the 5th and 7th weeks to identify gestational sac and fetal heart activity, and upon confirmation of this, the patient was thought to have clinical pregnancy.

Statistical Analysis

The 20th version of the licensed SPSS (Statistical Package for the Social Sciences) program (SPPS Inc. Chicago, USA) was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated using the Kolmogorov–Smirnov test. The sample t-test (student t-test) was used for the comparison of normally distributed data. The Mann–Whitney U test was used to compare data that did not

show normal distribution. The Chi-square test was used for the comparison of categorical data. P < 0.05 was found to be statistically significant.

Results

A total of 215 patients, 105 patients in the injury group and 110 patients in the control group were included in our study (Figure 1).

Both groups (injury and control groups) had similar characteristics in terms of age, duration of infertility, primary or secondary infertility, endometrial thickness on hCG administration day, and number and size of mature follicles (Tables 1 and 2). Both groups consisted of patients with infertility due to unknown cause, normal basal hormone levels, and with partners having normal spermiogram results according to the WHO criteria.

According to the results of the study, it was observed that 27 (25.7%) patients in the injury group and 19 (17.3%) patients in the control group could achieve pregnancy, 21 (20%) of these patients in the injury group and 14 (12.7%) patients in the control group were able to achieve clinical pregnancy (Table 3). As a result, although both pregnancy and clinical pregnancy rates were found to be increased in the injury group, this increase was not statistically significant (p = 0.131 for pregnancy rate; p = 0.545 for clinical pregnancy rate).

Table 1. Comparison of descriptive data of both groups

Variable	Injury group (mean ± SD)	Control group (mean ± SD)	P value
Age (years) [a]	28.50 ± 3.484	28.75 ± 4.165	0.709
Duration of infertility (years) [b]	3.30 ± 2.148	3.85 ± 2.675	0.236
Endometrial thickness on hCG day (millimeters) [b]	9.885 ± 2.218	9.432 ± 2.132	0.231
Number of mature follicles [b]	1.18 ± 0.458	1.14 ± 0.345	0.312
Mature follicle size (millimeters) [b]	18.75 ± 1.135	18.55 ± 1.168	0.813

[a] Student's t-test was used, [b] Mann–Witney U test was used

Table 2. Comparison of infertility types of two groups

Infertility type	Injury group (%)	Control group (%)	Total (%)
Primary infertility [c]	48 (45.7%)	40 (36.4%)	88 (40.9%)
Secondary infertility [c]	57 (54.3%)	70 (63.6)	127 (59.1%)
Total (%)	105 (100%)	110 (100%)	215 (100%)

[c] Chi-square test was used.

Table 3. Pregnancy and clinical pregnancy rates for both groups

	Injury group (%)	Control group (%)	Total (%)	P value
Pregnancy	27 (25.7%)	19 (17.3%)	46 (21.4%)	
No pregnancy	78 (74.3%)	91 (82.7%)	169 (78.6%)	0.131
Total (%)	105 (100%)	110 (100%)	215 (100%)	
Clinical pregnancy	21 (20%)	14 (12.7%)	35 (16.3%)	
No clinical pregnancy	84 (80%)	96 (87.3%)	180 (83.7%)	0.545
Total (%)	105 (100%)	110 (100%)	215 (100%)	

Chi-square test was used

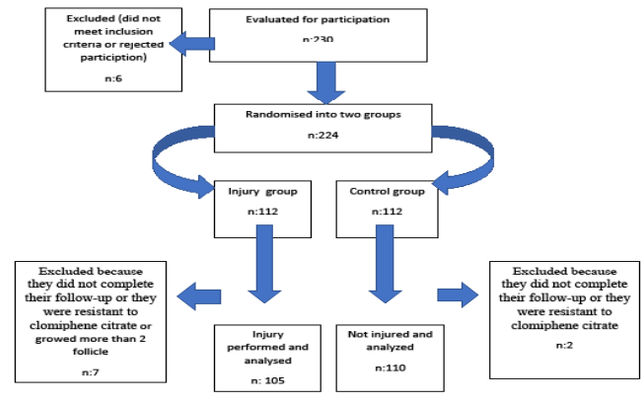

Figure 1. CONSORT flow diagram

Discussion

This study demonstrated that performing local endometrial injury in the luteal phase of the cycle before ovulation induction with clomiphene citrate and timed intercourse 36 hours after hCG administration, increased the rate of pregnancy and clinical pregnancy, but this increase was not statistically significant.

In the literature, it is seen that various procedures have been attempted to induce endometrial injury in infertility treatment using clomiphene citrate. It is seen that many different procedures, such as selected patient groups, method of injury and time of injury, timed intercourse after injury, or trial of intrauterine insemination (IUI) have been tried, different results have been obtained, and there is no clear consensus on these issues. We used a Novak curette for injury, because it is easy to use it and it can make enough injury even for one time.

In the study of Helmy et al., timed intercourse was planned by administering human chorionic gonadotropin (hCG) after ovulation induction with clomiphene citrate to patients with unexplained infertility similar to our study [2]. The endometrial injury was applied to the patients in the study group (n: 52) using a Pipelle catheter during the luteal phase of the previous cycle (between days 15 and 24), and a sham procedure was applied to the control group (n: 53) on the same days. Evaluation of the results showed that the rate of total pregnancy and clinical pregnancy were statistically significantly higher in the injury group [2]. When our results are compared with this study, which was planned with a similar method and the number of patients was much less than our study, we can say that although pregnancy rates are higher in the injury group numerically, our results are not statistically significant. Also, Helmy et al. found endometrial thickness on follicular maturation days similar in both groups like our study. Although there was no statistically significant difference in endometrial thickness between the two groups, we attributed the increase in pregnancy rates in the study group to the increase in endometrial receptivity.

In the study conducted by Ghuman et al., intrauterine insemination (IUI) was planned in a heterogeneous group (first, 2nd, 3rd and overall cycles included, n: 150) requiring IUI after ovulation induction with clomiphene citrate; however, unlike our study, 75 of them were examined in the same cycle using a Pipelle endometrium sampling catheter during the proliferative

phase and injury was applied, and IUI was administered with human chorionic gonadotropin (hCG) after ovulation [14]. On evaluation of the results, it was seen that the rates of pregnancy and clinical pregnancy increased in the study group, just like our results, but the results were not statistically significant [14]. They found endometrial thickness on hCG trigger day was significantly greater in the intervention group compared to control group, only in the first cycle ovulation induction, unlike our study.

In a randomized controlled study conducted by Maged et al., a total of 154 patients with unexplained infertility were subjected to IUI procedure following ovulation induction with clomiphene citrate and administration of human chorionic gonadotropin (hCG) for ovulation [15]. These patients were divided into two groups and one group underwent endometrial injury with a number 8 neonatal feeding tube, 24–36 hours before the IUI procedure. No additional intervention was made in the control group. When evaluating the results, it was seen that pregnancy rates were statistically significantly higher in the injury group. They were not investigated endometrial thickness and injury procedure relationship [15]. In our study, we preferred to apply the injury procedure during the luteal phase of the previous cycle so as to not damage the endometrium. Also, we used the Novac curette for injury. We can say that different types of injury procedures can make enough effect for endometrial injury like feeding tube, pipelle or curette.

On the other hand, in a randomized controlled study performed on 217 patients with unexplained infertility, Parsanezhad et al. added human menopausal gonadotropin with clomiphene citrate on the 6th–8th days of the cycle and spontaneously planned timed intercourse after ovulation [16]. After a spontaneous urinary LH peak was detected using a urinary kit, endometrial biopsy was performed with an endometrial Pipelle catheter or mock pipette in the pre-ovulation period, and endometrial injury was induced. When evaluating the results, it was observed that there was a statistically significant increase in pregnancy rates in the injury group when compared with the control group [16] . In many studies, especially in IVF patients, because the injury procedure performed on the day of oocyte collection traumatized the endometrium very much and there was no time for adequate repair, researchers prefer the injury procedure over the previous cycle [16-18]. Therefore, like Persanezhad et al. we preferred to make injury process in the cycle before ovulation induction. Also, they found endometrial thickness similar in both injury and not injury group, while pregnancy rates are increased in injury group, like our study. They attributed these results of endometrial injury to positive effects such as increased endometrial receptivity, increased decidualization, cytokine production, and gene expression.

As seen in the study, endometrial injury can increase the success of pregnancy after using clomiphene citrate in patients with unexplained infertility and timed intercourse after ovulation induction. Perhaps, this study will show that the negative effect of clomiphene citrate on the endometrium can be prevented through endometrial injury. Thus, clomiphene citrate, which is a very easy to use ovulation induction agent, can be made a preferred method in the treatment of infertility thanks to endometrial injury.

Conclusion

Considering all these studies, our study seems sufficient and comprehensive in terms of the number of patients when compared with other studies. However, when evaluating our results, it is seen that while there is an increase in the rate of pregnancy due to endometrial injury procedures, no statistically significant result was obtained. It seems that much larger and more comprehensive studies are needed to show that adding endometrial injury to treatment with clomiphene citrate, which is an extremely cost-effective and easy procedure, can actually increase pregnancy rates.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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